PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2000 (15.05.00)	
International application No. PCT/CH99/00476	**Applicant's or agent's file reference** 13-5
International filing date (day/month/year) 07 October 1999 (07.10.99)	**Priority date** (day/month/year) 07 October 1998 (07.10.98)
Applicant BEVILACQUA, Frédéric et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 April 2000 (10.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

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Translation
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 79 658 a/sk	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/07203	International filing date (*day/month/year*) 29 September 1999 (29.09.99)	Priority date (*day/month/year*) 30 September 1998 (30.09.98)
International Patent Classification (IPC) or national classification and IPC C07K 1/04		
Applicant MOLECULAR MACHINES & INDUSTRIES GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 April 2000 (19.04.00)	05 July 2000 (05.07.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/07203

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-9, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-9, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims		NO
Inventive step (IS)	Claims	1-9	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations

1. This report makes reference to the following documents:

D1: WO-A-98/41534 (BIOSEPRA & SEPRACOR) 24 September 1998 (1998-09-24)

D2: WO-A-97/19749 (P J DEHLINGER) 5 June 1997 (1997-06-05)

D3: WO-A-92/21079 (THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 26 November 1992 (1992-11-26).

2. The present application relates to a process for the solid-phase synthesis of substances in which the solid phase consists of two different substrates (e.g. needle tip and container wall), a reaction system and an analytical process for the chemical structure as well as the biological properties of the compounds obtained from the above process.

3. None of the prior art documents cited in the application or the international search report (D1 - D3) discloses a process for solid-phase synthesis

with the technical characteristic of a solid phase consisting of two different substrates. Therefore the claimed solid phase synthesis process (Claims 1-7), the reaction system on which this process is based (Claim 8) and the corresponding analytical process for chemical structures and biological properties (Claim 9) can be considered novel (PCT Article 33(2)).

The technical problem that the present application seeks to solve can be seen as that of making available a process that overcomes the disadvantages of the prior art processes with regard to the possibility of analysing the chemical structure and biological activity of the synthetic products of libraries of substances (e.g. the purity of substances, undesirable interactions during routine experiments etc.).

None of the documents cited in the prior art gives a qualified indication that would lead a person skilled in the art to the solution suggested here. Therefore the presence of an inventive step is also acknowledged for the subject matter of Claims 1-9.

Claims 1-9 can also be seen as meeting the requirements of PCT Article 33(4) with regard to industrial applicability.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. The reference to the German patent application 198 22 542.4 (page 7) contravenes the requirements of PCT Rule 5.1(a)(ii), according to which the source of the prior art, i.e. in this case the corresponding publication number of the Offenlegungsschrift, should be stated.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
13-5		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CH 99/ 00476	07/10/1999	07/10/1998
Applicant		
ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE etal.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract is changed as follows:

Line 5: delete from "(g1 and g2..." until line 6 "...the medium)"
Line 7: delete from "The spectral..." until line 9 "...is disclosed."
Line 14: delete from "Four embodiments..." until line 17 "...of the surface."

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 99/00476

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N21/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	F. BEVILACQUA ET AL: "In vivo local determination of tissue optical properties" SPIE, EUROPEAN BIOMEDICAL OPTICS, BIOS EUROPE 97, vol. 3194, 1997, pages 262-268, XP000866481 page 267, last paragraph page 265, line 7 -page 266, line 10 ---	1,12,14, 15
A	US 5 452 723 A (WU JUN ET AL) 26 September 1995 (1995-09-26) column 12, line 43 - line 54 column 10, line 21 - line 33 column 6, line 44 -column 7, line 15 --- -/--	1,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2000	16/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Verdoodt, E

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CON[redacted]ED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	P. MARQUET ET AL: "DETERMINATION OF REDUCED SCATTERING AND ABSORPTION COEFFICIENTS BY A SINGLE CHARGE-COUPLED-DEVICE ARRAY MEASUREMENT, PART I: comparison between experiments and simulations" OPTICAL ENGINEERING, vol. 34, no. 7, July 1995 (1995-07), pages 2055-2063, XP002129315 abstract page 2057, left-hand column, line 1 -page 2058, left-hand column, line 6 ---	1,14
A	D.R. WYMAN ET AL: "Similarity relations for the interaction parameters in radiation transport" APPLIED OPTICS, vol. 28, no. 24, 15 December 1989 (1989-12-15), pages 5243-5429, XP000086704 page 5245, right-hand column, line 1 -page 5246, left-hand column, line 2 abstract -----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/CH 99/00476

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5452723 A	26-09-1995	NONE	

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
13-5		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CH99/00476	07/10/1999	07/10/1998
International Patent Classification (IPC) or national classification and IPC G01N21/49		
Applicant ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 36 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/04/2000	01.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Purdie, D Telephone No. +49 89 2399 2187

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CH99/00476

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-25	as received on	21/11/2000	with letter of	17/11/2000

Claims, No.:

1-20	as received on	21/11/2000	with letter of	17/11/2000

Drawings, sheets:

1/15-15/15	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 8-11, 20.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 8-11, 20 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 12

	No:	Claims	1-7, 13-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-7, 12-18
Industrial applicability (IA)	Yes:	Claims	1-7, 12-18
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R It m I

Basis of the report

The amendments filed with the fax dated 17 November 2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The term "no support", as used below in this section, means no support in the application as originally filed.

Claim 1 No support has been found either for "by using optional signal processing .... illumination source or the detector" or for "precise".

Claim 3 No support has been found in the application as originally filed for the last four lines of this claim (see also claim 6, lines 10 and 11).

Claim 4 No support has been found for "MOS camera" (also claim 6, lines 12-14).

Claim 5 No support has been found for the "collimated or focused beam" of claim 4 being in contact with the turbid medium.

Claim 9 No support has been found for the functions A and B depending on the "sources and detector characteristics, and the refractive index of the sample".

In the description, no basis in the application as originally filed has been found for:

the wording on p1 describing with which domain of electromagnetic radiation the invention can operate ("that can be applied in the extended ... ten-electron-Volt."). UV radiation is strongly absorbed in any non-vacuum environment, for example, and there is nothing in the application as originally filed which suggests special provisions for the transmission of UV radiation. The light sources referred to in the application as originally filed (those on p10, lines 20-24, for example) are not generally applicable to the extreme ends of the region mentioned in the above mentioned wording.

"in parallel" on the second line of p6;

"generated locally" (p8);

"In a general situation ... spatially resolved reflectance" (p9);

the phase function generally depending on the dielectric properties and on the material microstructure (p9);

the removal of "Fig. 7" on p19 (line 11);

the removal of the expression after the word "quantity" on p23 (fourth line of type);

the removal of "f" and "h" from the line following equation (1.14) on p24.

The examination has been carried out as if none of the above amendements were made.

R It m III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No opinion with regard to novelty, inventiveness of industrial applicability can be established for any of claims 8 - 11 and claim 20. This is due to a lack of clarity in these claims:

Claim 8 Firstly, the dependancy of this claim is unclear. Claim 8 describes a method whereby "the processing of the spatially resolved reflectance data of claim 7 can be simplified and accelerated", and so, despite the wording of line 1 of the claim, it would appear that the claim can only be dependent on claim 7. The "spatially resolved reflectance data" and the "processing" thereof are features of claim 7 in as much as claim 7 includes all the features of those claims upon which it is dependent; neither of these features is to be found in the wording of claim 7, although both are found in claim 1. Further, it is not clear where in the methods according to any of claims 1 to 7 the steps of claim 8 are to be carried out. As they are carried out to "simplify and accelerate" the processing, it would seem that they must be performed somewhere within the processing procedure (although where is not clear). Despite this, a "computation is made from **the** data obtained by Monte Carlo simulations" (p31). This can only refer to the Monte Carlo simulations carried out in the method of claim 7, Monte Carlo simulations appearing here for the first time in the claims and being part of the "processing of the spatially resolved data". As this computation is made **from** this Monte Carlo data, it must be carried out **after** the "processing of the spatially resolved data", the very process the method steps of claim 7 seek to accelerate. This is paradoxical.

Claim 9 The dependancy of this claim suffers from the same clarity problems as claim 8 (see above). Further severe problems of clarity similar to those of claim 8 exist.

Claim 10 Claim 10 is dependent on claim 9. Due to the non-establishment of opinion for claim 9, no opinion can be established for claim 10.

Claim 11 It would appear that the function B in this claim is equal to the square root of R, and that μ_{a0} and μ_a have been erroneously transposed in the equation on line three of the claim. However, it is not clear how the difference $\Delta\mu_a = \mu_a - \mu_{a0}$ can be calculated

from the given quantity.

Claim 20 The claims define the matter for which protection is sought (Article 6 PCT). For a procedural (or method) claim this is normally done by formulating a series of method steps to be followed. This is not the case for this claim. For example, on p36 it is stated that "in this calibration procedure, the background light, measured with the light source turned off, must be subtracted from the signal". How this is to be interpreted as a step in the procedure is in no way clear. As a further remark, the procedure of claim 20 is said to be carried out "**optionally** with the apparatus of any of the claims 15, 16, 17 and 18". The method of claim 20 is however formulated by referring to these claims, a formulation which rules out their optional nature.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: F. BEVILACQUA ET AL: 'In vivo local determination of tissue optical properties' SPIE, EUROPEAN BIOMEDICAL OPTICS, BIOS EUROPE 97, vol. 3194, 1997, pages 262-268, XP000866481

Claim 1

Claim 1 describes a method for local and superficial characterization of a turbid medium. When the claim is reduced to its bare features it comprises the following:

measuring the spatially-resolved reflectance $R(\rho)$ of the turbid medium (ρ being the source-detector distance)by any means comprising an illumination beam as a source and an optical detector;

mathematically processing $R(\rho)$ to compute at least one of n, μ_a, μ_s', γ (n being the refractive index, μ_a the absorption coefficient, μ_s' the reduced scattering and γ the phase function parameter, all of the turbid medium), and/or variations of at least one of these.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses apply to D1) a method (see abstract) for local and superficial characterization of a turbid medium (biological tissues) comprising the steps of:

measuring the spatially-resolved reflectance of the turbid medium by a means comprising an illumination beam as a source and an optical detector (see, e.g., p266, first and second paragraphs in section 3.5);

and then mathematically processing the spatially-resolved reflectance to compute the reduced scattering coefficient and the absorption coefficient (see, e.g., p267, first paragraph).

Claim 1 is therefore not novel (Article 33(2) PCT).

The following claims are dependent on claim 1 and are also not novel (all references are to D1):

Claims 2-4: see, e.g., p263.

Claim 5: see fig. 2, p263.

Claim 6: see, e.g., p263, in particular fig. 1.

Claim 7: see, e.g., p264, Section 2.3 "Monte Carlo Simulations", also "Introduction", p262.

Claim 13: see, e.g., p266, section 3.5 "*In vivo* measurements on brain tissues".

Claim 14: see, e.g., p267, line 1.

The following claim is dependent on claim 1 and cannot be considered inventive (Article 33(3) PCT):

Claim 12: replacing the laser diodes of fig. 2 on p263 of D1 with broadband sources and introduction of a spectrograph before the detector cannot be considered inventive. Wavelength selection is already included in D1 (p263, second paragraph).

Claim 15

The document D1 is regarded as being the closest prior art to the subject-matter of claim 15, and discloses an apparatus for local and superficial characterization of a turbid medium comprising (the references in parentheses apply to D1):

a source (see "laser diode" in fig. 2, p263), a detection unit (see "linear CCD" in Fig. 2, p263), reference means (see Fig. 2), signal processing means (see "PC" in Fig. 2), a probe comprising at least one optical fiber connecting said source unit to the turbid medium and at least one optical fiber connecting the turbid medium to the said detection unit (see "probe" in Fig. 2. Also Fig. 1 and text on p263), where the distance between the source and the detector is close to one transport

mean free path (see, e.g., abstract).

Claim 15 is thus not novel.

Claim 16

The apparatus described in D1 comprises an illuminating source, at least one detector, a signal processing means and a reference means (all illustrated in Fig. 2 on p263). The distance between the source and the detector is close to one transport mean free path.

Claim 16 is thus not novel.

Claim 17

The apparatus described in D1 comprises (see fig. 2, p263):

a collimated beam (generated by the laser diode) used as illuminating source, an optical detector for the detection unit ("CCD"), a fixed optical system for the illuminating source ("optical switch"), a fixed optical system for the optical detector ("microscope objective", for example), signal processing means ("PC") and reference means, where the distance between the source and the detector is close to one transport mean free path.

Claim 17 is therefore not novel.

Claim 18

Claim 18 is not novel (see fig. 1 on p263 of D1).

Re Item VII

Certain defects in the international application

The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

Equation 1.10 has been corrected, apparently to correct a mistake in the original (equation 9 on p15 of the application as originally filed). The equation still does not appear to be correct, however.

R Item VIII

Certain observations on the international application

The claims are not clear and are thus not in accord with Article 6 PCT.

Throughout the claims several terms and expressions are given in inverted commas. It is not clear that there is any reason for this and it leads to a lack of clarity.

The method claims are in general unclear. The applicant is referred to the comments made with regard to claim 20 in section III above. Method steps cannot be phrased in terms of what **can** be done (see, for example, the second line of claim 8) or what **may** be done (see, for example, claim 20, p36, line 12) as this sort of formulation does not define a scope of protection.

Various obscure and therefore unclear functions appear in the claims: in particular, "any mathematical combination of the (aforementioned in the claim) two quantities" in claim 8; "A" and "B" in claim 9; and *"f"* and *"h"* in claim 10.

Claim 1

The semi-colon after "parameters" (second last line, p26) should be a comma (see also the part of claim 8 on p31). In the same line, "said" should not be present and in the last line, "optical coefficients" should apparently read "parameters".

It is not clear what "the phase function p" is.

In section V, in order to examine the novelty of claim 1, it has been stripped down to its essential features. It can thus be seen that claim 1 does not fulfill the conciseness requirements of Article 6 PCT. Moreover, much of the excess text is vague and unclear (see,for example, "said "model" **incorporates** a Legendre polynomial development to the second order of the said "phase function"").

Claim 6

It is not clear what the "second optical system" is, nor what the "first one" is (line 8)

Claim 10

The word "claims" on the first line of claim 10 should read "claim", and the word "of"

after "γ" should apparently not be present.

Claim 11

Only one instance of the words "can be" should be present in the forth line of claim 11.

Claims 15-17

Although claims 15-17 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

The words "using the method of claim 1 to 3, 5 or 7 to 14" should not be present in apparatus claim 15. Claims 16 and 17 contain similar unsuitable expressions.

It is not clear that there is support in the description for the "reference means", as required by Art. 6 PCT. The word "reference" appears in Fig. 5a, but this does not help much with regard to this obscurity. It is not clear whether the apparatus defined by claim 15 has one or two "reference means".

The apparatus claims 15-17 are defined in terms of "one transport mean free path". Although "transport mean free path" is a known term within a certain context, its use here does not clearly define the apparatus.

Claim 18

It is not clear whether claim 18 refers to one apparatus or three apparatuses. The full stop after 2mm should not be present.

Contrary to the requirements of Art. 6 PCT, there does not seem to be any support in the description for the statement in claim 9 that "the quantity $\delta/\delta\rho \surd R(\rho, \mu_s', \gamma)$ ... depends weakly on the absorption coefficient μ_a for $0.3 < \rho\mu_s' < 5$."